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Sex-specific and gender-specific aspects in patient-reported outcomes



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ABSTRACT

Patient-reported outcomes (PROs) are important tools in patient-centred medicine and allow for individual assessment of symptom burden and aspects of patients' quality of life. While sex and gender differences have emerged in preclinical and clinical medicine, these differences are not adequately represented in the development and use of patient-reported outcome measures. However, even in personalised approaches, undesirable biases may occur when samples are unbalanced for certain characteristics, such as sex or gender. This review summarises the current status of the literature and trends in PROs with a focus on sex and gender aspects.

BACKGROUND

There is an increasing interest in research about the influence of sex and gender on health in general. Differences in gender identity and biological sex are postulated to impact the course and perception of a disease trajectory and eventually influence diagnosis and treatment.¹ Both sex (defined by the biological underlying genetics) and gender (a person's psychological sense of their identity) may therefore influence prevalence, onset, trajectory, treatment response and prognosis in cancer.² There is also growing evidence for sex and gender having an impact on outcome differences in cardiovascular, neurological and autoimmune diseases, including disease course and treatment response. Yet, there are no mandatory requirements to investigate the impact of sex and gender on drug receptivity or adverse effects in clinical study design. Also in preclinical studies and drug development, it is common protocol to use animals of one sex only. In clinical studies, due to anticipated risks of pregnancy or hormonal imbalance, women are frequently under-represented, which translates into biased interpretation of results and pharmacokinetics.³ Yet, sex-related factors, as hormonal regulation, and gender-related factors, as behavioural differences in stress perception, lifestyle and risk-seeking behaviour, appear to be relevant influencers of disease perception and outcome. Recent publications additionally discuss interrelation

between sex and gender, postulating gender-triggered epigenetic effects to modulate the expression of biological sex.⁴ Eventually, differences arising from sex and gender gaps may lead to a differential use of medical services, insufficient treatment of symptoms or greater toxicity of medication.^{5,6} To date, there is still little knowledge about the influence of the overall gender spectrum in medicine, which includes transgender, non-binary and genderqueer (TNBGQ) persons. Due to sparse publications on TNBGQ and outcome studies, this review will mainly focus on the female-male dichotomy for patient-reported outcomes (PROs). The influence of gender on the diseases examined here will however be discussed.

The understanding of patients' symptoms in the course of any disease is crucial for patient-centred medicine. However, some symptoms are often under-reported by the patient and may also be underestimated by physicians, leading to undertreatment of patients.⁷ One potential cause for underestimated symptoms is the lack of time for deeper discussions or the inability to address psychological symptoms, which are often considered more complex than pharmacologically treatable physical symptoms.⁸ Addressing symptoms actively and in a structured manner can help patients reporting subjective burden. Likewise, to monitor the symptom load and response to treatment in the course of a disease, systematic assessments are useful and help to evaluate psychological or physical symptoms, as well as the subjective burden of the patient.

PROs reflect the patient's subjective view on symptoms, quality of life and burden and therefore allow for patient-centred and individualised management. They are captured by patient-reported outcome measures (PROMs), covering several areas of potential symptoms in the course of a disease. Most importantly, emotional burden can be covered, including sensitive symptoms that patients might not wish to address actively

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in daily medical routine. Allowing a patient to express symptoms that are most relevant to him/her is therefore important, and open questions may represent a good start to an assessment dialogue with the patient. However, a standardised format is more consistent at actively inquiring about a broad range of symptoms and other aspects of disease burden. Often, patients experience more symptoms than they state.⁹

PATIENT-REPORTED OUTCOME MEASURES

Many validated assessment tools are available and have been used recently in routine clinical practice and clinical studies, especially in the field of oncology. They mainly address symptoms and symptom burden, functional status, health-related quality of life (HRQoL), health behaviours and patients' healthcare experience. The term 'quality of life' has not yet been well defined and is commonly used as umbrella term to describe a person's individual perception of well-being, including physical but also emotional and social aspects of life.¹⁰ This concept has become an important focus in healthcare and has become a frequently assessed endpoint in clinical studies, captured by PROMs. Since patient-reported symptoms are intrinsically subjective, it is crucial to use the same validated tool for longitudinal assessments in order to reduce the chances of bias occurring between timepoints of data collection. [Table 1](#) summarises characteristics of some of the most important PROMs in clinical medicine.

Given the documented effects of sex and gender on health and drug management, it is necessary to explore further the influence of sex and gender on PROs, mirroring symptom perception and reporting. The existence of sex-specific/gender-specific questionnaires covering gynaecological or andrological diseases is obvious, but sex and gender differences in PRO from other common diseases have been under-researched. To date, most guidelines of PROM assessments do not take into consideration that sex and gender differences can arise as an undesirable bias and might influence the results and interpretation of the collected information.¹¹ The purpose of the present review is to evaluate the current status of sex-specific and gender-specific outcome differences in PROs. For this review, we conducted a PubMed literature search of all relevant studies published through June 2020 using any of the following key words: PROs, sex/gender differences, symptom assessment, symptom severity, pain, nausea, vomiting, functional status, fatigue, depression sleep, HRQoL, functional status, health behaviours, and patient experience, cancer diseases, non-cancer diseases.

PROS IN ONCOLOGY

Cancer, as well as anticancer therapy, can result in impaired quality of life, increased symptom load and/or psychosocial burden. Advocates within oncology have called for the systematic use of PROMs to detect problems that are assessed directly by the patient.¹² Although

often not investigated as primary objective, publications of PROM assessments in oncology did assess sex as a main variable, and the European Society for Medical Oncology (ESMO) recently published a consensus paper, confirming a universal male predominance for most cancers, and advocating for specific attention to sex and gender medicine in oncological practice with the aim to optimise treatment for patients.¹³ Sex-specific cancer biology plays a crucial role in the development but also the treatment responses in cancer. Y-chromosome-located oncogenes or hormonal growth influence may contribute to differential cancer disposition.^{14 15} On the contrary, gender aspects have been identified as contributors to higher cancer risks, as alcohol consumption and smoking habits.¹⁶ Overall, gender constructs and biological sex both influence disease development. Yet, perception of disease and symptoms are relevant factors to diagnosis and treatment as well and might be captured differently in PROM based on sex and gender. Several studies with comparative subgroup analyses found worse self-reported outcomes in PRO for female patients with regard to symptom burden and perception, despite surviving longer than male. A large, population-based analysis of PROM-assessed symptoms in patients with oesophageal cancer under curative treatment, which used the Edmonton Symptom Assessment System (ESAS),¹⁷ revealed an overall high symptom burden with severe symptoms in up to 50% of patients for anorexia, tiredness and overall poor well-being. Among the characteristics associated with symptom severity, female sex was consistently present.¹⁸ In a study of 120 patients with colorectal cancer that completed PROMs for symptom burden, the severity score for worrying and lack of energy was significantly higher in women compared with men.¹⁹ Similarly, in a cohort of more than 400 patients with melanoma, female patients reported significantly more anxiety over a 2-year prospective follow-up assessment period compared with male patients.²⁰ In a population of patients with advanced cancer, including lung, pancreatic or oesophageal tumours, male sex predicted a better emotional well-being, assessed by the Functional Assessment of Cancer Therapy questionnaire (FACT-G).^{21 22} In another cohort of mixed cancer patients with terminal disease, however, symptom burden for pain perception was significantly correlated with male gender.²³ In brain tumours, the sequelae lead to a broad spectrum of complex central symptoms, including neurocognitive impairment, personality change and motor issues. All of these problems can have a great impact on HRQoL and activities of daily living, as well as devastating social and economic consequences. This indicates that the assessment of PROs is especially important in order to address all needs experienced by patients with brain tumour. In a systematic review of 10 studies, all using HRQoL outcomes for supportive care interventions in a wide array of different tumour types,²⁴ the majority of participants was male, with the exception of 3 studies.^{25–27} Likewise, a large meta-analysis of 15 randomised controlled trials (RCTs)

Table 1 PROMs in medicine (selection)

PROMs	Items (N)	Subscales	Disease
Global HRQoL			
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core Module (EORTC-QLQ-C30)	30	Functional scale Symptom scale Single items Overall Health and QoL	Adult cancer patients (disease-specific modules available)
Functional Assessment of Cancer Therapy—General (FACT-G)	27	Physical well-being Social/family well-being Emotional well-being Functional well-being	Adult cancer patients (disease-specific modules available)
Palliative Care Outcome Scale (POS)	11	Physical, psychological, social and spiritual symptoms Open question	Palliative patient population (staff version available)
Symptom assessment—general			
MD Anderson Symptom Inventory (MDASI)	13	Clinical symptoms Interference items	Adult cancer patients (disease-specific modules available)
Edmonton Symptom Assessment System (ESAS)	10 items		Pan-cancer
Brief Symptom Inventory (BSI)	53 items	Primary symptom Indices of distress	Psychological symptoms (disease/non-patient)
Symptom assessment—focused			
Brief Pain Inventory (BPI)		Pain intensity Pain interference	Pain
Hospital Anxiety and Depression Scale (HADS)	14 items	HADS Anxiety score HADS Depression score Total HADS score	Adult cancer patients
NCCN Distress Thermometer (DTherm)	1 item	Psychological distress	Adult cancer patients
Functional Assessment of Cancer Therapy—Fatigue (FACIT-F)			
The Pittsburgh Sleep Quality Index (PSQI)	19 items	Subjective sleep quality Sleep latency Sleep duration Habitual sleep efficiency Sleep disturbances Use of sleeping medication Daytime dysfunction	Adult cancer patients

Continued

Table 1 Continued

PROMs	Items (N)	Subscales	Disease
European Organisation for Research and Treatment of Cancer (EORTC) QLQ-BN20	20 items	Clinical Psychosocial	Brain tumour patients
Functional status			
Karnofsky Performance Status		Performance status scale	Adult cancer patients
Functional Assessment of Cancer Therapy-cognitive function (FACT-COG)	37 items	Perceived cognitive impairments cognitive abilities Impact of perceived cognitive impairment on QoL Other cognitive function	Adult cancer patients
Montreal Cognitive Assessment (MoCA)	30-point screening tool	Attention and concentration Executive functions Memory Language Visuoconstructional skills Conceptual thinking Calculation Orientation	Brain tumour patients
EORTC Sexual Health Questionnaire (SHQ-22)	22 items	Sexual desire Sexual activity Pain	Adult cancer patients
Health behaviours			
Morisky Medication Adherence Scale	8 items	Medication taking behaviour	Adult cancer patients
Behavioural Risk Factor Surveillance System (BRFSS)	14 core sections	Smoking Alcohol use Physical activity Diet Chronic health conditions Immunisation Breast and cervical cancer screening Prostate cancer screening Colorectal cancer screening HIV/AIDS	Adult cancer patients
Patient's healthcare experience			

Continued

Table 1 Continued	
PROMs	Items (N)
The Cancer Patient Experiences Questionnaire (CPEQ)	69 items
	<div> <div>Inpatient/ outpatient experiences</div> <div> <div>▲ Nurse contact</div> <div>▲ Doctor contact</div> <div>▲ Information</div> <div>▲ Organisation</div> <div>▲ Patient safety</div> <div>▲ Contact with next of kin</div> <div>Hospital standard</div> </div> </div>
	<div> <div>(7 items)</div> <div>(7 items)</div> <div>(7 items)</div> <div>(6 items)</div> <div>(3 items)</div> <div>(3 items)</div> <div>(4 items)</div> </div>
Disease	Adult cancer patients

HRQoL, health-related quality of life; PROMs, patient-reported outcome measures; QoL, quality of life.

with 5217 patients assessing the added value of HRQoL as prognostic marker for overall survival and progression-free survival demonstrated that the majority of included patients overall were male (61 %),²⁸ pointing towards an imbalance of sex. Importantly, in studies that did stratify for gender and sex differences, outcome differences by sex emerged, often with a worse outcome for female patients. In a recent Swedish study, female patients with lower grade glioma were reported to have a worse performance status preoperatively, which resulted in a delayed diagnostic work-up.²⁹ On therapeutic levels, toxicity of the alkylating chemotherapy with temozolomide—although administered body surface adapted—was consistently reported to be higher in female patients.^{30 31} Interestingly, altered body image perception in patients with primary brain tumour did not differ by sex,³² whereas in a non-brain tumour study, changes of body image were seen to have a larger emotional impact on female patients compared with male patients.³³ Overall, most PROs published in cancer did not stratify for sex, despite its well-known role as genetic and hormonal disease modifier, contributing to an imbalance in these assessments. Subgroup analyses for sex however confirm a differential outcome in symptom perception and ultimately outcome and treatment. Gender, as factor influencing social roles among others, was not in the focus of the analysed publications, despite being a variable that influences not only patient's behaviour and response to the diagnosis but eventually the interpretation of PROs by the clinicians.

Non-cancer diseases

Although PROs have emerged mainly in routine clinical practice and clinical trials in oncology, there are several non-oncological diseases for which PROs are used. Especially in the cardiovascular disease spectrum, several studies have assessed sex on the one hand and gender on the other hand as outcome variable. In heart diseases, sex-related influencing factors, as hormonal oestrogen protection, have been described.³⁴ Despite this protective variable, women with ischaemic heart disease are more often underdiagnosed and less likely to receive classic treatment.^{35 36} Moreover, the risk for recurrence of ischaemic heart disease eventually increases in patients with feminine personality traits and is independent of the female sex,³⁷ distinctly pointing towards a gender bias. Finally, the sex of the physician eventually is an influencing factor as well. Mortality rates of female patients with myocardial infarction increase when treated by male physicians compared with female physicians.³⁸ With regard to PROs, data on sex and gender aspects is less available. Despite a lower age-adjusted incidence of stroke in women, female patients who had a stroke usually experience a worse outcome with regard to HRQoL, activity limitations or depression compared with male patients who had a stroke.^{39–41} In studies specifically designed to assess patient-reported HRQoL by sex, women showed a worse outcome in activities of daily living, assessed by the Barthel Index or Stroke-specific quality of life scores.⁴²

In another study using the European Quality of Life-5 Dimensions (EQ-5D) instrument in more than 1000 patients who had a stroke, women scored a significantly lower quality of life at 3 months and 12 months post-stroke.⁴³

Similarly, in cardiovascular assessments, comparative PROMs for patients with atrial fibrillation showed a sex/gender imbalance with women reporting more severe perception of symptoms, poorer quality of life and increased symptoms of anxiety and depression.⁴⁴ While one can postulate that physical and psychological symptoms are intertwined in this cardiac population, the reasons for the sex/gender imbalance demonstrated in this study remained unclear.

PROs in palliative care

PROs are appreciated tools in palliative care, where patient-centered outcome shifts even more in the focus and symptom burden is assessed in a population with a broad variety of primary diseases. Sex and gender aspects are usually not in the focus of PRO assessments. In a register-based study of patients with cancer referred to palliative care who completed the European Organisation for Research and Treatment of Cancer (EORTC)-QLQ-C15-PAL, associations with symptoms and sex showed increased risk of nausea for women, whereas other symptoms, such as pain or sleeplessness, showed a stronger association with age than sex.⁴⁵ In contrast, a secondary analysis of an RCT including 350 patients suffering from lung or gastrointestinal cancers and receiving early palliative care reported better quality of life and lower depression scores in self-reported assessments of male patients with lung cancer.⁴⁶ Conversely, male patients with advanced cancer reported dyspnoea more frequently^{47 48} and greater severity of dyspnoea relative to female patients.⁴⁹ Results regarding fatigue in palliative care patients have been inconsistent with some studies reporting higher fatigue in female palliative care patients^{50 51} and other studies documenting lower levels of fatigue in females⁵² relative to male palliative care patients. The same study found terminally ill female patients with cancer to be in a more positive mood compared with male patients of the same cohort. Interestingly, when comparing symptom distress between male and female palliative care patients, female patients reported higher levels of distress related to pain, nausea and fatigue relative to their male counterparts.⁵³ The same study found that females had to report higher levels of distress in order to receive adequate pain treatment.

Caregiver-reported outcomes

In a study of caregivers of palliative care patients, taking care of a loved one is associated with high distress due to the patient's progressive health deterioration, anticipatory grief about the inevitable death, adoption of supportive responsibilities, financial stressors and disruption of the caregiver's social and personal life.⁵⁴ During the illness trajectory, caregivers frequently experience

pain, fatigue, sleep disturbances and depression.^{55–57} Although gender roles are changing and an increasing number of men are assuming caregiving roles, caregiving responsibilities still disproportionately affect women.⁵⁸ Women assisted with more personal care were involved in more caregiving tasks and provided more caregiving hours than men.⁵⁹ However, while earlier studies identified poorer health outcomes for female caregivers, including increased psychological distress and physical health problems,^{60 61} results from more recent studies indicate a decline of this gender difference in caregiving variables.⁵⁹ It is assumed that female and male caregivers all experience grief, distress and depression.⁶² Correspondingly, the retrospective assessment of psychosocial outcomes by gender most commonly found no significant influence of gender on outcome scores when specifically assessed.^{63–65} However, in studies demonstrating a gender-shifted outcome, female gender was associated with a higher level of distress.^{66 67} A postulated explanation included perception of insufficient caring and self-efficacy in female carers.⁶⁸ Women relative to men are at greater risk for experiencing emotional burdens of caregiving.⁶⁹ One possible explanation for this consistent finding is that women often assume the responsibilities of full-time employment simultaneously with child-rearing and household maintenance. Thus, the risk of competing responsibilities is greater in women than in men, which can result in a sense of being 'entrapped in informal care'.^{63 70} Yet, in caregivers of children with cancer, no differences were found between paternal or maternal proxy scorings with regard to distress, indicating that gender in this context is not of major importance.⁷¹ Overall, although sex and gender are not always well separable, self-reported outcome measures in caregivers are more often determined by gender aspects and behavioural characteristics.

Table 2 lists publications that included PROs by sex/gender (not exhaustive).

DISCUSSION

Although sex and gender differences in disease prevalence, treatment tolerability and overall treatment outcomes have been reported increasingly in the last years, information on sex-specific and gender-specific aspects in PROMs has remained sparse.

In this review, we found that, although often not investigated as primary objective, most studies evaluating PROMs in oncological and non-oncological diseases have assessed sex as a main variable. Informations on gender are often lacking, although several reports include gender as a synonym term for sex when stratifying globally for a male-female dichotomy. Evaluating PROs for sex and gender differences displays consistent evidence that women and men report differently their physical symptoms, HRQoL and psychosocial burden. Most studies found sex/gender differences for outcome reports, both for physical symptoms, such as

Table 2 PRO by sex and gender

Reference	Publication	PRO measure	Outcomes
Appellos <i>et al</i> ³⁹	A review on sex differences in stroke treatment – and outcome	–	Post-stroke depression and low quality of life seem to be more common among women.
Armstrong <i>et al</i> ³⁰	Risk analysis of severe myelotoxicity with temozolomide: the effects of clinical and genetic factors	–	Risk of developing myelotoxicity ranged from 0% to 33% (male) and from 0% to 100% (females).
Bushnell <i>et al</i> ⁴³	Sex differences in quality of life after ischaemic stroke	European Quality of Life-5 Dimensions (EQ-5D)	Women have worse QoL than men up to 12 months after stroke, even after adjusting for important sociodemographic variables, stroke severity and disability.
Carey and Posavac ⁵²	Holistic care in a cancer care centre	Profile of Moods States (POMS)	Women reported a better and more positive mood compared with male patients and scored lower anxiety and fatigue.
Carstam <i>et al</i> ²⁹	Socioeconomic factors affect treatment delivery for patients with low grade glioma: a Swedish population-based study	–	Female sex, low income and low education showed worse preoperative performance status.
Falk <i>et al</i> ⁵³	Differences in symptom distress based on gender and palliative care designation among hospitalised patients	Edmonton Symptom Assessment Scale (ESAS)	Females reported higher levels of symptom distress than males related to pain, fatigue and nausea. When comparing symptom distress between males and females with documentation pertaining to symptoms, there were significant differences implying that females had to report higher levels of symptom distress than males in order to have their symptoms documented.
Gargano and Reeves ⁴²	Sex differences in stroke recovery and stroke-specific quality of life: results from a statewide stroke registry	Barthel Index Stroke-Specific Quality of Life Questionnaire	Compared with males, female stroke survivors had lower functional recovery and poorer quality of life 3 months postdischarge. These differences were not explained by females' greater age at stroke onset or other demographic or clinical characteristics.
Gleason <i>et al</i> ⁴⁴	Association of sex and atrial fibrillation therapies with patient-reported outcomes	Atrial Fibrillation Effect on Quality of Life (AFELT) Patient-Reported Outcome Measurement Information System-29 (PROMIS)	Women were more likely to report poorer functional status (–2.63, 95% CI –3.86 to –1.40) and poorer aF-related quality of life, higher anxiety (2.33, 95% CI 1.07 to 3.59), higher symptoms of depression (1.48, 95% CI 0.31 to 2.65) and aF symptom severity (0.29, 95% CI 0.07 to 0.52).
Gupta <i>et al</i> ¹⁸	Patient-reported symptoms for oesophageal cancer patients undergoing curative intent treatment	Edmonton Symptom Assessment System (ESAS)	Characteristics associated with severe scores for all symptoms included female sex, high comorbidity, lower socioeconomic status, urban residence and symptom assessment temporally close to diagnosis.
Hansen <i>et al</i> ⁴⁵	Age, cancer site and gender associations with symptoms and problems in specialised palliative care: a large, nationwide, register-based study	EORTC-QLQ-C15-PAL	Gender, age and cancer diagnosis were significantly associated with most symptoms/problems. The strongest associations between symptoms/problems and gender and age, respectively, were increased risk of nausea in women, as well as increased risk of poor physical function and reduced risk of sleeplessness and pain with increasing age.
Kanbayashi <i>et al</i> ²³	Statistical validation of the relationships of cancer pain relief with various factors using ordered logistic regression analysis	–	Pain was significantly correlated with gender ($p=0.006$) and bone metastases ($p=0.005$).

Continued

Table 2 Continued

Reference	Publication	PRO measure	Outcomes
Matthews <i>et al</i> ⁶⁹	Family caregivers and indicators of cancer-related distress	Quality of Life-Family Tool (QOL-F)	Female sex, less practice of healthy behaviours, greater number of patient care needs and pessimistic expectations (all p s <0.05) also were significant predictors for distress and emotional burden.
Mercadante <i>et al</i> ⁴⁹	The course of symptom frequency and intensity in advanced cancer patients followed at home	Karnofsky Performance Score	Dyspnoea was more severe in males at K50 (p <0.008).
Nipp <i>et al</i> ⁴⁶	Differential effects of early palliative care based on the age and sex of patients with advanced cancer from a randomised controlled trial	Functional Assessment of Cancer Therapy-General (FACT-G) Patient Health Questionnaire 9 (PHQ-9)	Male patients with lung cancer assigned to EPC reported better QoL (FACT-G: $B=9.31$; $p=0.01$) and lower depression scores (PHQ-9: $B=-2.82$; $p=0.02$), but the effects of EPC on these outcomes were not significant for female patients.
Pottie <i>et al</i> ⁶²	Informal caregiving of hospice patients	–	Caregiver characteristics (ie, ethnicity, gender, age, relationship with patient) were not found to be associated with caregiver outcomes.
Röhl <i>et al</i> ¹⁹	Symptoms during chemotherapy in colorectal cancer patients	Memorial Symptom Assessment Scale (MSAS) Karnofsky Performance Status (KPS)	Age, sex, educational level, performance status, treatment intent and type of chemotherapy were significantly associated with symptom severity throughout the chemotherapy trajectory.
Zeng <i>et al</i> ⁵⁰	Fatigue in advanced cancer patients attending an outpatient palliative radiotherapy clinic as screened by the Edmonton Symptom Assessment System	Karnofsky Performance Score	A low KPS (p <0.0001), being female ($p=0.0056$), or being referred for bone metastases ($p=0.0185$) significantly correlated with higher levels of fatigue.
Zimmermann <i>et al</i> ⁵¹	Predictors of symptom severity and response in patients with metastatic cancer	Edmonton Symptom Assessment Scale (ESAS)	Symptom improvement was independently predicted by worse baseline EDS score and female gender.
Zimmermann <i>et al</i> ²²	Determinants of quality of life in patients with advanced cancer	Functional Assessment of Cancer Therapy-General (FACT-G) Functional Assessment of Chronic Illness Therapy-Spiritual Well-being (FACIT-Sp)	Male patients reported better emotional well-being.

aF, atrial fibrillation; EDS, ESAS distress score; EORTC-QLQ, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EPC, early palliative care; PRO, patient-reported outcome.

nausea, dyspnoea or pain, and for psychological symptoms, such as anxiety and mood. Often, the outcomes in female patients were worse compared with male. Sex differences in human physiology as well as the fact that women are often under-represented in clinical trials as discussed above may explain why women report more adverse events to medication compared with men.⁷² For instance, previous studies have postulated different pain thresholds between genders.⁷³ On the contrary, a meta-analysis of studies analysing the use and response of men and women to opioids for pain control found evidence that sex did not affect response to opioids 30 min after application, but that women self-administered lower daily doses of opioids.⁷⁴ Another perspective recognises the multimodal perception of pain, acknowledging that pain is sustained not only by physical but also by emotional burden. It follows that outcomes may vary depending on the proposed and accepted treatment options, including psychological and spiritual care.⁷⁵ Finally, the role of the assessing person, physician or nurse should not be underestimated either. Sex or gender of the diagnostician can influence the outcome of a disease, as for women with cardiac infarction described to have higher mortality rates when treated by male doctors.³⁸ Likewise, the perception of the sex/gender of the patient by the physician can influence a diagnostic assessment as well. Male patients with depressive disorders seeking treatment are less likely to be diagnosed with major depression, even with similar assessment scores as female comparators.⁷⁶ Therefore, several factors may influence differential symptom perception and therefore reported outcomes between sexes and genders. Either way, treatment based on unbalanced studies can eventually lead to insufficient or excessive medication or treatment in general. Yet, most guidelines for treatment of diseases are identical for men and women. Evaluating whether sex-specific treatment modifications can improve outcome should be in the focus of future studies.

Limitations of this study arise from the fact that gender differences were not the primary endpoint in most reviewed publications and that both PROM tools and investigated patient populations were heterogeneous. While there is an increasing number in publications assessing epidemiological, diagnostic or therapeutic differences for sex and gender nowadays, the role of gender bias in outcome measures reported by patients themselves is under-investigated to date. Furthermore, data beyond the binary gender spectrum is missing in the current literature as well. These limitations underline the need to consider prospective collection of gender-specific aspects in PROs in comparable, balanced patient populations. Correspondingly, algorithms for clinical trials and routine clinical practice should include assessments validated for gender or sex differences.

Recently, normative data for the general population in Europe, Canada and the USA has been assembled by

means of EORTC-QLQ-C30 collection⁷⁷ and stratified by sex. Here, men reported better scores for overall quality of life and emotional function compared with women, which was also observed in other norm data studies,^{78 79} confirming sex and gender differences beyond disease. Hence, the collection of normative data might represent an important step towards a better understanding of gender and sex influence in PROs. Other approaches that might be helpful include the use of tools that help with the design of studies, incorporating sex and gender questions with possible impact on results, assisting in identifying undesirable biases due to gender imbalances and pointing out desirable biases that would help with targeted treatment for each gender.^{11 80} In patient-centred care with appropriate, focused reaction to patient-reported symptoms and symptom burden, it is warranted to include further differential assessments by gender. Physicians and medical personnel should be aware of sex and gender differences not only in pharmacokinetics or disease trajectories but also on the level of symptom perception.

CONCLUSION

In the process of development and validation of PROMs, it is crucial to have a well-balanced population of the gender spectrum, assessing differences between male and female reports and including gender identities beyond the binary concept. When PROMs are used in clinical practice, comparative analyses between the groups should be included early in order to detect potential gender-specific outcome differences.

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